Complete response and long-term survival after stereotactic body radiotherapy in a patient with liver metastasis from α-fetoprotein-producing gastric cancer: A case report

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Abstract. α-Fetoprotein (AFP)-producing gastric carcinoma (GC) (AFPGC) is a special subtype of GC that is clinically characterized by a high incidence of liver metastasis and poor prognosis. The present study reported the case of a patient with AFPGC who showed complete response (CR) after stereotactic body radiotherapy (SBRT) for liver metastasis. A 76-year-old male patient underwent total gastrectomy with D2 lymph node dissection for GC. The excised tumor was diagnosed as AFPGC due to the patient's high serum AFP level (3,763 ng/ml) and AFP expression on immunohistochemistry. The patient was diagnosed with liver metastasis two months after the surgery. ^{18}F-fluorodeoxyglucose positron emission tomography indicated that the metastasis was a single recurrent focus. Although the patient underwent seven cycles of chemotherapy with S-1-based regimens, the metastatic tumor showed only a minor response despite the decrease in serum AFP levels. To realize high-quality disease control, SBRT was performed on the liver tumor (total dose of 48 Gy in four fractions). The metastasis showed a significant response two weeks after the completion of SBRT and CR two years later. CR was sustained and the patient survived with no evidence of recurrence 62 months after the diagnosis of liver metastasis. Literature data on the efficacy of radiotherapy for liver metastasis from AFPGC remain scarce. The present case report suggests that SBRT has high efficacy for oligometastatic diseases and may be included as an indication for the treatment of liver metastasis from AFPGC.

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Abbreviations: AFP, α-fetoprotein; AFPGC, AFP-producing GC; CR, complete response; CT, computed tomography; FDG, fluorodeoxyglucose; GC, gastric carcinoma; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; LM, liver metastasis; PET, positron emission tomography; SBRT, stereotactic body radiotherapy

Key words: α-fetoprotein, complete response, gastric cancer, liver metastasis, stereotactic body radiotherapy

Introduction

α-Fetoprotein (AFP) is a 70-kDa glycoprotein that was first identified as a fetus-specific protein in human serum in 1956 (1). Although physiologically produced by fetal liver and yolk sac, AFP is also secreted by several kinds of tumor cells. Hepatocellular carcinoma (HCC) and yolk sac tumor are diseases that are associated with the aberrant production of AFP (2), and in those cases, AFP is clinically used as a biomarker for diagnosis, treatment evaluation and surveillance of disease progression or relapse. Certain gastric carcinomas (GCs) also express AFP and patients with GC of this type have high serum AFP levels (3). Such AFP-producing GCs (AFPGCs) may be clinically discriminated from common GCs by their hepatocyte-like appearance in histology, high potential for venous invasion in pathology and poor clinical prognosis (4-6). Earlier studies have reported that patients with AFPGC are prone to having liver metastasis (LM) synchronously or metachronously (5-8). Thus, controlling LM is critical to improve the survival of patients with AFPGC. However, the treatment strategy has remained unestablished because AFPGC is a relatively rare disease.

Chemotherapy is generally selected as the treatment of LM from AFPGC because multiple metastatic foci are observed in most cases and LM is considered a result of hematogenous spreading. However, no recommendable chemotherapeutic regimen has been established to date. On the other hand, surgery is adopted for single or oligometastasis to the liver. Unfortunately, the outcomes of surgical resection are unsatisfactory (9,10).

Radiotherapy, another local therapeutic option, is rarely indicated for LM from AFPGC because of a lack of evidence of the radiosensitivity of this tumor and a significant risk of radiation-induced liver diseases. However, advances in irradiation

technology, including stereotactic body radiotherapy (SBRT), have expanded the indications for radiotherapy and upgraded this therapy into a recommendable alternative for the treatment of HCC, a primary liver cancer (11,12). However, there is currently no information on the efficacy of SBRT for LM from AFPGC.

The present study reported the case of a 76-year-old male patient with AFPGC who underwent SBRT for LM after gastrectomy and showed a complete response (CR). The treatment strategy for LM from AFPGC was also discussed with a literature review.

Case report

A 76-year-old male patient underwent follow-up endoscopy for a small gastric polyp at Sanjo General Hospital (Sanjo, Japan) in February 2018. The endoscopy revealed type 1 gastric carcinoma (Japanese Classification of Gastric Carcinoma) (13) in the upper body of the stomach. The biopsy specimens of the tumor histologically showed poorly differentiated adenocarcinoma, solid type. The patient underwent total gastrectomy with D2 lymph node dissection and the surgery ended in complete resection (Fig. 1). Due to the unique gross tumor form and the hepatoid cellular appearance on microscopy with hematoxylin and eosin staining (4) (Fig. 2A), AFPGC was suspected and serum AFP levels were measured. AFP levels were as high as 3,763 ng/ml (normal range, 0-10 ng/ml) in preoperative serum and rapidly decreased to 2,567 ng/ml on postoperative day 27. Immunohistochemistry (IHC) using anti-human AFP monoclonal antibody (cat. no. 738291; Nichirei Bioscience) showed diffuse and strong immunoreactivity of tumor cells, confirming the diagnosis of AFPGC (Fig. 2B). IHC staining was performed with an automated IHC analyzer (Histostainer 48A; Nichirei Bioscience) according to the manufacturer's instructions.

Serum AFP levels rose to 4,484 ng/ml two months after the surgery, during which the patient was undergoing adjuvant chemotherapy with S-1 (tegafur/gimeracil/oteracil). Contrast-enhanced computed tomography (CT) revealed metastasis to the posterior segment of the liver and ^{18}F-fluorodeoxyglucose positron emission tomography indicated that the LM was a single recurrent focus (Fig. 3).

Systemic chemotherapy was started on the basis of the 'watch-and-wait' strategy (14). The patient underwent chemotherapy with one cycle of the SP regimen (S-1/cisplatin) and six cycles of the SOX regimen (S-1/oxaliplatin). Although serum AFP levels steadily decreased with the chemotherapeutic cycles and no new metastasis appeared during the treatment, the extent of shrinkage of the metastatic tumor was modest (Fig. 4A).

It was hypothesized that the introduction of local therapy would enable high-quality disease control and prolong patient survival. Treatment options for local control, including surgery, radiofrequency ablation and transcatheter embolization, were thus proposed. The patient finally selected radiotherapy because he preferred minimally invasive therapy and underwent SBRT (dose covering 90% of the planning target volume, 48 Gy; maximal point dose, 61.3 Gy; in four fractions) for LM on an outpatient basis.

CT revealed a significant response two weeks after the completion of SBRT (Fig. 4B). Magnetic resonance imaging

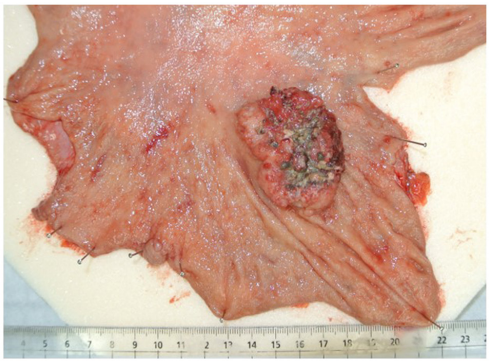

Figure 1. Gross appearance of the excised tumor. The tumor was 5.3x4.0 cm in size and located in the upper body of the stomach. The tumor appeared like a large plateau-like mass with a coarse nodular surface.

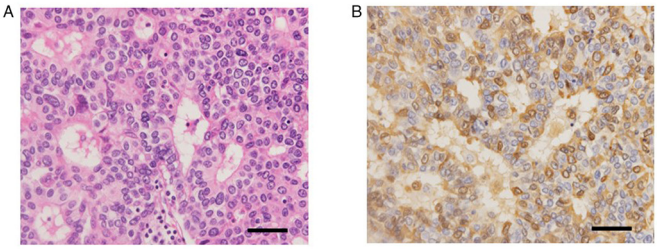

Figure 2. Histological findings of the excised tumor. (A) Pathological examination with hematoxylin and eosin staining showed that the tumor was composed of polygonal cells with abundant eosinophilic cytoplasm. (B) Immunohistochemical analysis using a monoclonal antibody specific for human α-fetoprotein revealed diffuse and strong immunoreactivity of tumor cells (original magnification, x400; scale bars, 50 μm).

demonstrated that the metastasis developed to radiological CR two years later and sustained CR thereafter (Fig. 4C). Serum AFP levels also continued to decrease and were normalized seven months after the start of SBRT. The time course of serum AFP level changes is shown in Fig. 5. The patient has been followed up thereafter and is surviving with no evidence of recurrence 62 months after the diagnosis of LM.

Literature review

To select studies addressing radiotherapy for AFPGC, a literature search was performed using the PubMed database, designating 'alpha-fetoprotein/AFP', 'esophagogastric cancer/stomach cancer' and 'radiotherapy/radiation' as the key words. The search was not limited to LM because it focused on the efficacy of radiotherapy for AFPGC. The search provided 33 reports that were published in English between January 1, 1970 and April 30, 2023; however, careful examination by three researchers (TK, YM and TT) revealed that only two reports mentioned radiotherapy for AFPGC and were in accordance with the research purpose of the present study. One was a case report of a patient with AFPGC in whom hilar lymph node recurrence showed CR after external beam radiotherapy (10). The other was a report of a patient with AFP-producing Siewert type I esophageal adenocarcinoma (15). The patient underwent proton beam therapy for the primary tumor and the metastases (paracardial lymph nodes and LM). In this case, although new

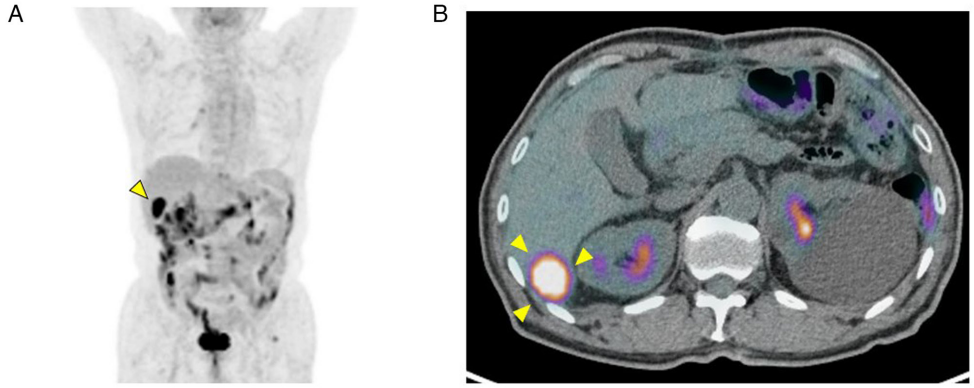

Figure 3. FDG-PET images. PET-CT revealed one significant active deposit in the liver (arrowheads). (A) Numerous intermediately active nodules in the maximal intensity projection were non-specific accumulations of the FDG metabolites in the feces. (B) PET-CT showed a single metastatic nodule (2.5 cm in diameter) with high metabolic activity (standardized uptake value, 10.4) in the posterior segment of the liver. FDG, ^{18}F-fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

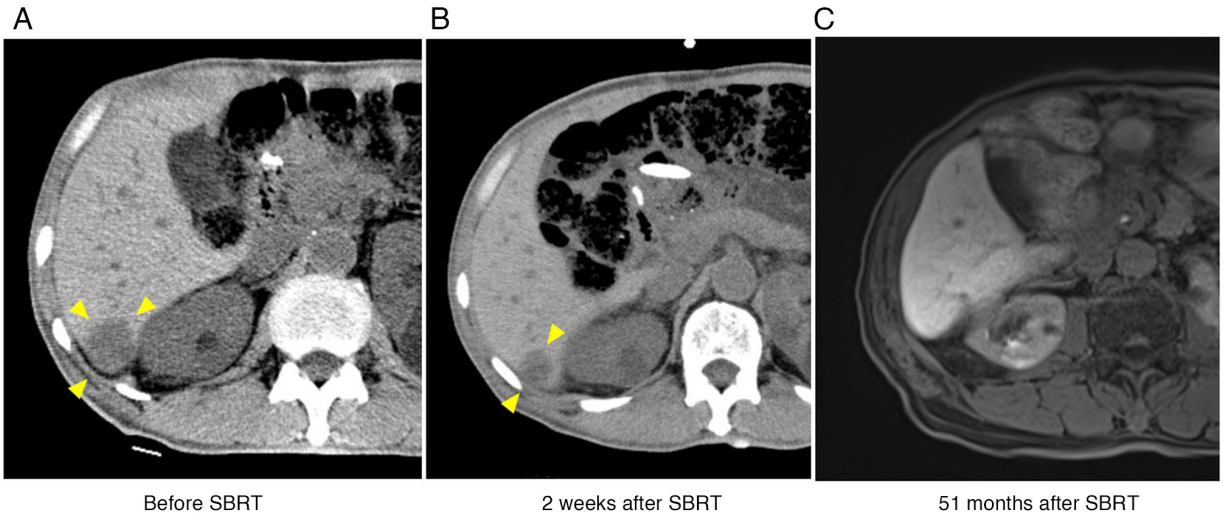

Figure 4. CT and MRI of the metastatic liver tumor. (A) CT revealed that the metastatic liver tumor showed no significant change in size after S-1-based chemotherapy despite the decrease in serum α-fetoprotein level. (B) The metastatic liver tumor showed partial response two weeks after the completion of SBRT. (C) MRI conducted 51 months after SRBT demonstrated sustained CR with partial liver atrophy in the irradiated field. Arrowheads indicate the metastatic tumor. CT, computed tomography; CR, complete response; MRI, magnetic resonance imaging; SBRT, stereotactic body radiotherapy.

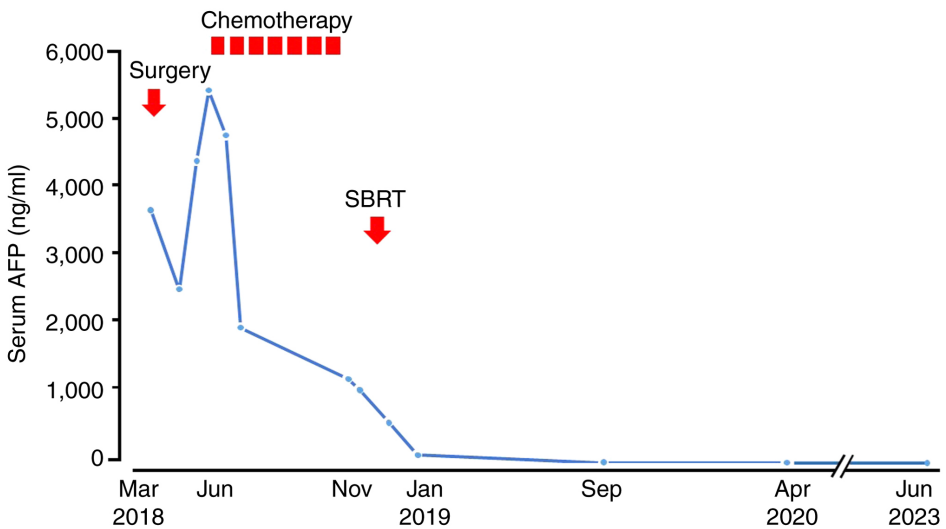

Figure 5. Time course of serum AFP levels and treatments of the patient. The serum AFP levels transiently decreased after tumor resection but rose again two months after surgery. Serum AFP levels returned to normal after SBRT and remained in the normal range from then on. AFP, α-fetoprotein. SBRT, stereotactic body radiotherapy.

lesions appeared immediately after a significant response, all tumors including the new lesions finally showed CR with multimodal therapy. A summary of the clinicopathological characteristics of the previously reported cases in comparison with the present case is presented in Table I.

Discussion

The present study reported on the case of a patient with AFPGC who has been surviving for five years following SBRT for LM. Regardless of the number of metastatic nodules, chemotherapy is the standard treatment for LM from GC (16) because LM is considered one of the clinical presentations resulting from the systemic dissemination of cancer cells and numerous patients with GC and LM are presumed to have subclinical minute metastases and to be at significant risk of a second recurrence.

Kodera *et al* (17) published a literature review on hepatectomy for LM from GC to clarify the efficacy of the surgery. They found 17 evaluable studies on this topic and comprehensively analyzed the survival of 515 eligible patients. Although the reported median survival widely varied from 9 to 38 months among the studies, 97 patients survived for five years or longer: The five-year overall survival was 18.8%. On the basis of these findings, the authors concluded that hepatectomy may be one of the treatment options for LM from GC in selected patients and to be considered particularly in solitary metastasis because 61% of patients included in their study had a single LM.

Shirasu *et al* (18) published a retrospective study addressing the timing of surgery for LM from GC. In that study, 24 patients with GC and liver oligometastasis (two or three metastases) who underwent treatment for LM were enrolled and divided into the hepatectomy group (n=9) and the chemotherapy group (n=15) on the basis of the initial treatment for LM. The median overall survival of the hepatectomy group was 24 months, being shorter than that of the chemotherapy group (38 months). They also found that the chemotherapy group included three patients who underwent conversion hepatectomy (hepatectomy following initial chemotherapy) and the survival of the conversion hepatectomy patients was excellent, with all three surviving in the follow-up period.

The abovementioned studies provide clinically important points regarding the treatment decision-making for LM from GC, i.e., chemotherapy is recommended in general as an initial treatment for LM from GC, and hepatectomy may be considered for selected patients, particularly those presenting with single or oligo liver metastasis who show a significant response following the preceding chemotherapy.

In the present case, SBRT was selected as an additional local therapy instead of hepatectomy. This choice was based on the patient's preference for low invasiveness. Clinical evidence of the efficacy of radiotherapy for LM is much less than that of surgery. In a literature review performed as part of the present study, no articles focusing on LM from GC were found. However, several pivotal studies have given us a hint that SBRT may be a rational therapy for patients with LM. A multi-institutional phase I/II study from the US (19) showed the safety and effectiveness of high-dose SBRT (60 Gy) in 47 patients with liver oligometastasis; a serious adverse event was reported in only one patient, and the two-year in-field

Table I. Summary of reported cases of radiotherapy for α-fetoprotein-producing esophagogastric adenocarcinoma.

Author, year	Age at diagnosis, years	Sex	Primary	Target	Radiotherapy	Total dose, Gy	Concurrent or post-radiation chemotherapy	Response	Survival after initial treatment, months	(Refs.)
Asahi, 2016	60	M	Stomach	Hilar lymph node metastasis	EBRT	60	Yes	CR[a]	102	(10)
Miyazaki, 2018	50	M	Lower esophagus	Primary tumor, paracardial lymph node metastasis and liver metastases	PBT	72.6	Yes	NE	50	(15)
Current case	76	M	Stomach	Liver metastasis	SBRT	48	No	CR	62	-

[a]Of target lesions. CR, complete response; EBRT, external beam radiotherapy; M, male; NE, not evaluable; PBT, proton beam radiotherapy; SBRT, stereotactic body radiotherapy.

control rate was as high as 92%. Furthermore, there was only one randomized phase II study that addressed the impact of SBRT on the survival of patients with oligometastatic cancer (20). Overall survival, which was set as the primary endpoint, was compared between the palliative radiation group and the SBRT with the radical doses (30-60 Gy) group in that study. The SBRT group showed longer overall survival than the palliative radiation group (41 vs. 28 months, median survival time), although the difference was not statistically significant. The abovementioned findings have demonstrated that SBRT has high local control ability for LM, suggesting that the high-level local disease control by SBRT may contribute to prolonging survival even in patients with LM.

Although SBRT resulted in CR in the present case, it remains elusive whether the high efficacy of SBRT in this patient with AFPGC can be generalized in LM from common types of GCs. Radiosensitivity is less clinically important in SBRT than in conventional radiotherapy because SBRT is a type of radioablative therapy that uses high-dose irradiation. However, the radiosensitivity of various tumors may have to be taken into consideration when selecting radiotherapy as a cancer treatment option. The current literature review revealed that data on the radiosensitivity of AFPGC are scarce: There are only two papers reporting the outcomes for patients with AFPGC who underwent radiotherapy. Although publication bias should be considered, it is noteworthy that the two patients showed a good response to radiotherapy.

Germ cell tumors, including yolk sac tumors, are representative malignancies that have high radiosensitivity. AFP is a fetal protein that is produced in the yolk sac and fetal liver. The fact that germ cell tumor and AFPGC share a common ontogenetic protein expression allows for the hypothesis that AFPGC cells may acquire radiosensitivity in the process of malignant transformation. Indeed, Ushiku *et al* (21) have shown that spalt-like transcription factor 4, an embryonic stem cell marker, is expressed in AFPGCs, as well as fetal stomach and germ cell tumors, and have claimed that AFPGC cells are characterized by the phenotype of retrodifferentiation into fetal gut cells. The molecular mechanisms underlying AFPGC occurrence remain elusive. More clinical data are needed to determine whether AFPGC is radiosensitive.

In conclusion, the current study presented a case of LM from AFPGC. The LM showed CR to SBRT and the patient has been surviving for five years after the diagnosis of LM. Despite being an anecdotal case, this case report offers clues that point to the possibility of the application of SBRT to AFPGC and implies that this tumor may be radiosensitive. Because AFPGC is rare, clinical trials to clarify the efficacy of radiotherapy for this disease are not feasible. Further accumulation of clinical data on a case-by-case basis is necessary to confirm the efficacy of SBRT for AFPGC.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TK, YM and TT were the attending physicians and cooperatively conducted the literature review. KN designed this study and collected the data on this case report. TK and YM drafted the manuscript. YM, KN and TT prepared the figures included in the manuscript. MN was responsible for the pathological diagnosis. TK and KN checked and confirmed the authenticity of the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the case report and all accompanying images.

Competing interests

The authors declare that they have no competing interests.

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